10 57. The method of claim 56, wherein said labeled unique sequence high complexity nucleic acid probe comprises fragments complementary to a single chromosome, fragments complementary to a subregion of a single chromosome, fragments complementary to a genome or fragments complementary to a subregion of a genome.

11 58. The method of claim 50, wherein the interphase chromosomal material is interphase chromosomal DNA.--

REMARKS

Entry of the foregoing, reconsideration and reexamination of the above-identified application are respectfully requested.

Claims 1, 48 and 50 have been amended to make clear that the chromosomal material of interest is present in a morphologically identifiable chromosome or cell nucleus during the hybridization. Support for this recitation may be found in the instant specification and in the applications from which priority is claimed.

In considering the support for this amendment, it is important to keep in mind that the invention is directed to the field of cytogenetics (page 2, lines 2-3; page 1, lines 10-12; page 1, lines 6-8)[1]. As such, the claims would be interpreted by cytogeneticists, cytologists and pathologists. Persons skilled in those arts must routinely

[1]Throughout the remainder of these remarks, the first citation refers to the passage in the specification of the present application and the continuations from which priority is claimed as continuation, and the second and third citations refer to the corresponding passage in the specification of the two earliest filed applications, i.e., Serial No. 06/937,793, filed December 4, 1986 and Serial No. 06/819,314, filed January 16, 1986, respectively.

make morphological assessments of chromosomes and cell nuclei, as discussed at page 5, lines 3-6 (page 4, lines 7-8; page 4, lines 1-3), concerning chromosomal morphology. Thus, it is a term readily understood by those skilled in the art.

The specification as originally filed makes clear that the target nucleic acid is present in a "morphologically identifiable chromosome or cell nucleus" at the very least by the recitation that "the target nucleic acid remains in its natural biological setting, e.g., DNA in chromosomes or cell nuclei (albeit fixed or altered by preparative techniques)" for in situ hybridization (page 8, lines 20-24; page 6, lines 20-23; page 6, lines 11-14). This makes clear that the chromosomal material is present in a "morphologically identifiable chromosome or cell nucleus" during its contact with the unique sequence high complexity probe. Thus, at the very least based upon this passage, it is evident that the chromosomal material is present in a "morphologically identifiable chromosome or cell nucleus" during the method of staining.

This amendment makes clear that the targeted chromosomal material is stained while the chromosomal material is still present in a morphologically identifiable chromosome or cell nucleus. As discussed at page 83, lines 7-15 (page 27, line 22, through page 28, line 7; page 26, line 23, through page 27, line 7), in situ hybridization includes the step of "(3) hybridization of the heterogeneous mixture of probe to the DNA in the biological structure or tissue" which is now defined in the claims as "a morphologically identifiable chromosome or cell nucleus." That the morphological detail is retained is also seen from page 85, lines 8-18 (page 29, lines 8-15; page 28, lines 8-15), where it is stated

that "chromosomes" are frequently treated with agents to remove proteins prior to hybridization, but that care must be exercised to avoid "unacceptable loss of morphological detail."

Moreover, one skilled in the art would recognize that the material is still present in a morphologically identifiable chromosome or cell nucleus for the method staining as claimed in claim 50 because the chromosomal material is interphase chromosomal DNA. This is further clarified in the specification, which states at page 27, lines 1-5 (page 10, lines 19-24; page 10, lines 11-16):

> Preferably, the staining reagents of the invention are applied to interphase or metaphase chromosomal DNA by in situ hybridization, and the chromosomes are identified or classified, i.e., karyotyped, by detecting the presence of the label, such as biotin or ^{3}H, on the nucleic acid fragments comprising the staining reagent.

Because the in situ hybridization is done using interphase chromosomal DNA, one skilled in the art would recognize that it must be present in a morphologically identifiable cell nucleus.

The specification further states at from page 83, lines 7-15 (page 27, line 22 to page 28, line 9; page 26, line 23 to page 22, line 7):

> Generally in situ hybridization comprises the following major steps: (1) fixation of tissue or biological structure to be examined, (2) prehybridization treatment of the biological structure to increase accessibility of target DNA, and to reduce nonspecific binding, (3) hybridization of the heterogeneous mixture of probe to the DNA in the biological structure or tissue; (4) posthybridization washes to remove probe not bound in specific hybrids, and (5) detection of the hybridized probes of the heterogeneous mixture.

That in situ hybridization is described as involving the steps of "fixation of tissue or biological structure" and "hybridization of the heterogeneous mixture of probe to the DNA in the biological structure or tissue" would teach to the skilled artisan that "the chromosomal material is present in a morphologically identifiable cell nucleus" during the method of staining as claimed.

Claim 49 has been deleted and claims 1 and 48 have also been amended to recite that the chromosomal material is "interphase" chromosomal material. Support for this amendment may be found at the very least at page 2, lines 11-14 (page 10, lines 19-24; page 11, line 24 - page 12, line 2).

Claim 1 has also been amended to recite that the chromosomal material and nucleic acid probe are employed in in situ hybridization. Support for this recitation may be found at the very least at page 21, lines 20-21, and from page 82, Section IV (page 10, lines 19-24 and from page 27, Section IV; starting from page 26, Section IV).

New claims 51-58 have also been added. Support for claims 51 and 55 may be found at the very least at page 22, lines 18-20 (page 2, lines 10-16; page 2, lines 3-9). Support for claims 52 and 56 may be found at the very least at pages 80-82, Section III (page 11, lines 11-18, and pages 24-26, Section III; page 11, lines 1-11, and pages 24-25, Section III). Support for claims 53 and 57 may be found at the very least at page 29, lines 17; page 45, lines 19-20; the sentence bridging pages 45 and 46; page 46, lines 9-10; page 51, lines 2-4; and pages 59-67, Section IA (page 11, lines 1-5; page 10, lines 17-21).

Support for claims 54 and 58 may be found at the very least at page 27, lines 1-5 (page 10, lines 19-24; page 10, lines 11-16).

Support for the instant amendments may thus be found in the instant application as well as Application Nos. 937,793 and 819,314, from which priority is claimed.

Claims 1 and 48-50 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Weissman et al in view of Lichter et al and Croco. This rejection is respectfully traversed.

As acknowledged by the Examiner, Weissman et al fails to disclose or even suggest a method of staining targeted interphase chromosomal material or genetic rearrangements associated with chromosome 3 and/or chromosome 17. In contradistinction to the instant invention, Weissman discloses only mapping to metaphase spreads (*see,* for example, Figure 5, Section VI and Example XI). That interphase chromosomal material could be reliably stained in a morphologically identifiable chromosome or cell nucleus in a method as claimed is in no way taught or even suggested by Weissman. Weissman further fails to disclose or even suggest a method of staining wherein the targeted chromosomal material is a genetic rearrangement associated with chromosome 3 and/or chromosome 17, as claimed by applicants.

In view of the deficiencies of Weissman, Lichter et al is cited as teaching interphase target assays and Croco is cited as disclosing chromosome 3 and 17 translocation targets. However, neither Lichter et al nor Croco is prior art to applicants' claimed invention.

The claims of record are entitled to the priority dates of January 16, 1986 and December 4, 1986, in view of the fact that support for the claims may be found in these earlier applications from which priority is claimed.

For example, support for claims 1, 48 and 50 may be found at the very least in Application Serial No. 937,793, filed December 4, 1986, at pages 8-15 and pages 32-39. Support for these claims may also be found at the very least in Application Serial No. 819,314, filed January 16, 1986, at pages 11-14 and pages 31-38. Support for the recitation that the genetic rearrangement is associated with chromosome 3 and/or chromosome 17 is implicit in the description that the staining reagents useful in the invention are specific to single chromosomes at page 11, lines 1-5 of Application Serial No. 937,793 and at page 10, lines 17-21 of Application Serial No. 819,314. One skilled in the art would understand the generic description of staining targeted chromosomal material to detect genetic rearrangements to describe each of the chromosomes, including chromosomes 3 and 17, as being the targeted material. Support for the newly added recitations and newly added claims is indicated *supra*.

In view of the fact that support may be found in the instant application, which is identical to the series of applications from which priority is claimed as a divisional and continuation, and support may be found in the 06/937,793 and 06/819,314 applications filed in 1986 from which priority is claimed as a continuation-in-part, Lichter et al published in 1988 and Croco having a 1989 priority date and an issue date of 1993 are not

proper prior art references. The combination of Lichter et al and Croco with Weissman is thus improper.

Withdrawal of the rejection of the claims as being unpatentable over Weissman in view of Lichter and Croco is thus respectfully requested and believed to be in order.

Withdrawal of these rejections is thus respectfully requested and believed to be in order.

Further and favorable action in the form of a Notice of Allowance is respectfully requested. Such action is believed to be in order.

In the event that there are any questions relating to this response, or to the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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